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Specific adolescent prodromal symptoms associated with onset of psychosis in the Northern Finland Birth Cohort 1986

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Abstract

Background: Several psychological symptoms in adolescence associate with later development of psychosis. However, it is unclear which symptoms specifically predict psychotic disorders rather than psychiatric disorders in general. We conducted a prospective study comparing how specific adolescent psychotic-like symptoms, predicted psychotic and non-psychotic hospital-treated psychiatric disorders in the population-based Northern Finland Birth Cohort 1986 (NFBC1986).

Methods: At age 15–16 years, 6632 members of the NFBC1986 completed the PROD-screen questionnaire. New hospital-treated mental disorders of the NFBC1986 participants were detected between age 17 and 30 years from the Finnish Care Register for Health Care. Multiple covariates were used in the analysis.

Results: During the follow-up, 1.1% of the participants developed a psychotic and 3.2% a non-psychotic psychiatric disorder. Three symptoms were specifically associated with onset of psychosis compared to non-psychotic psychiatric disorders: 'Difficulty in controlling one's speech, behaviour or facial expression while communicating' (adjusted OR 4.00; 95% CI 1.66–9.92), 'Difficulties in understanding written text or heard speech' (OR 2.25; 1.12–4.51), and 'Difficulty or uncertainty in making contact with other people' (OR 2.20; 1.03–4.67). Of these, the first one remained statistically significant after Bonferroni correction for multiple comparisons.

Conclusion: To our knowledge, this is the first general-population-based prospective study exploring psychiatric symptoms predicting the onset of hospital-treated first-episode psychosis in comparison to non-psychotic disorders. We found three symptoms related with difficulties in social interaction which predicted onset of psychosis. This is a novel finding and should be replicated.

KEYWORDS
adolescent, birth cohort, general population, predictor, prodromal, psychosis

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1 | INTRODUCTION

Schizophrenia and other psychotic disorders are one of the most severe causes of worldwide burden of disease (GBD, 2017). At least some psychoses are considered neurodevelopmental disorders which overtly manifest in adolescence and early adulthood (Bearden & Forsyth, 2018; Kauppi et al., 2015; Murray et al., 2017). Both positive prodromal symptoms (Lindgren et al., 2021; Tso et al., 2017) and negative features (Devoe et al., 2018) have been found to precede psychoses in clinical samples (Fusar-Poli et al., 2020), though the predictiveness of existing criteria among adolescents is questionable (Lång et al., 2021).

Prodromal symptoms of psychosis have been studied retrospectively in large population samples and in genetic high-risk cohorts, where they are found to precede the transition to a psychotic disorder by several years (Oliver et al., 2020). Also, in a prospective general population sample with 3000 adolescents from Germany, negative and disorganized features predicted the onset of first-episode psychosis (Dominguez et al., 2010). Furthermore, in the Dunedin Study birth cohort with originally about 1000 participants, self-reported psychotic symptoms at age 11, both positive and negative, were predictive of schizophreniform psychosis at age 26 (Poulton et al., 2000). In a later analysis of the same sample, however, psychotic-like symptoms in childhood did not specifically predict schizophrenia but were associated with general mental health problems in adulthood (Fisher et al., 2013).

It is thus unclear whether psychotic-like symptoms are relatively specific precursors of later psychoses, or general markers of vulnerability to mental health problems. In the present study, putative prodromal symptoms of psychosis in adolescence were therefore studied as predictors of first onset of hospital-treated psychosis in the general-population-based Northern Finland Birth Cohort 1986, using non-psychotic psychiatric patients as controls, and in this way differentiating between symptoms specifically predictive of psychotic disorders and symptoms generally predictive of psychiatric disorders (Mäki et al., 2014).

2 | MATERIAL AND METHODS

2.1 | Setting

Members of the Northern Finland Birth Cohort 1986 (NFBC1986; $N = 9479$), an unselected general population cohort (Järvelin et al., 1993; University of Oulu, 1986), were re-examined at the age of 15–16 years (Hurtig et al., 2011; Taanila et al., 2004). This field study, conducted between April 2001 and February 2002, included the 21-item PROD-screen questionnaire (Heinimaa et al., 2003). Data on NFBC1986 participants' hospital-treated mental disorders in 2003–2016 were retrieved from the Finnish Care Register for Health Care (CRHC). Both the cohort participants and their parents gave informed, written consent to retrieve, link, and use their questionnaire data. The study was approved by the Ethical Committee of The Northern Ostrobothnia Hospital District and was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013).

2.2 | PROD-screen

The PROD-screen is a questionnaire developed for inquiring about psychotic-like symptoms possibly indicating heightened risk for psychosis (Heinimaa et al., 2003). The self-report form has 21 items which are derived from previous instruments, such as the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS; Häfner et al., 1992), the Bonn Scale for the Assessment of Basic Symptoms (BSABS; Gross et al., 1987) and the Structured Interview for Prodromal Symptoms (SIPS; McGlashan et al., 1998) and indirectly, the Comprehensive Assessment of At-risk Mental States (CAARMS; Yung et al., 1996). Response alternatives are Yes or No. In the present study, the PROD-screen addressed self-reported symptoms reported by the adolescent (aged 15–16 years) cohort members within the last 6 months. Every item of the PROD-screen was considered as a separate risk indicator for later first-episode psychosis (Table 3).

2.3 | Outcome variables

All hospital treated psychiatric diagnoses of the members of NFBC1986 appearing in the CRHC between the years 2003 and 2016 for any psychiatric disorder treatment as an inpatient were identified by record linkage using personal identification codes. Outcome variables of psychotic disorders and non-psychotic psychiatric disorders included the whole follow-up period from baseline 2003 to the end of follow-up 2016. The cumulative incidence of first-episode psychosis by gender is described in Figure 1. The nationwide CRHC covers all mental and general hospitals, as well as beds in local health centres and private hospitals nationwide. In this study, psychotic disorders included all non-organic psychoses; that is, schizophrenia (ICD-10 code F20), schizoaffective psychosis (F25), affective psychosis (F30.2, F31.5, F32.3, F33.3, and F31.2), and other psychoses (ICD-10 codes F22F24, F26–F29, F30.2, F31.2, F31.5, F32.3, and F33.3). All other psychiatric disorders (with an F code) were considered non-psychotic disorders, excluding organic disorders (F00–F09) and developmental disorders (F70–F79). Non-psychotic diagnoses included substance use disorders (F10–F19), non-psychotic mood disorders (F30.0, F30.1, F30.8–F31.1, F31.3–F31.4, F31.6–F31.9, F32.0–F32.2, F32.4–F33.2, F33.4–F33.9, and F34–F39), and other non-psychotic disorders (F21, F40–F69, and F80–F99).

We grouped participants into the exclusive groups (1) any psychotic disorder, regardless of presence of non-psychotic psychiatric disorders, (2) any non-psychotic psychiatric disorder, (3) no psychiatric disorder. Lifetime CRHC data were also used to remove participants with any previous psychiatric disorders from the follow-up analyses.

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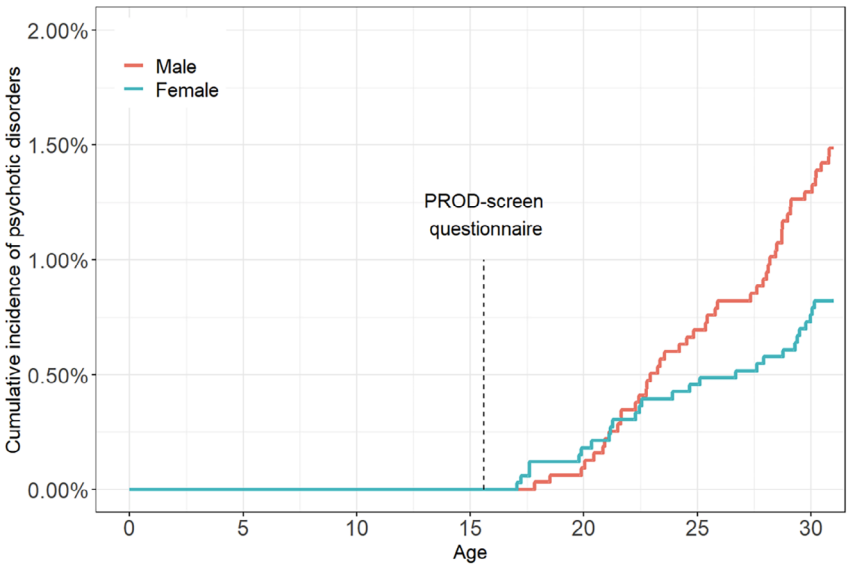

FIGURE 1 Cumulative incidences of first-episode psychosis between ages 17 and 32 (years 2003–2016) in the Northern Finland 1986 Birth Cohort, by gender. PROD-screen questionnaire was filled in at age 15–16 (2001–2002), and the follow up of psychotic disorders started at 2003 (at age 17 years)

2.4 | Confounding factors

Gender was used as a confounding factor in all analyses. Any *psychiatric disorder in either parent* according to CRHC data dating back to 1971 (yes vs. no) was also considered a confounding factor, as was *parental educational level* (highest parental education; basic at <10 years, secondary at 10–12 years, and tertiary at >12 years) at the time of the field study in adolescence, as reported by the parents. *Family structure* (living with two parents vs. other) and *cannabis use* (never vs. ever) in adolescence were also considered confounding factors in the analyses and were obtained from the self-report questionnaire containing the PROD-screen. All these variables chosen as confounders are known to be risk factors for psychosis (Radua et al., 2018), and their distributions by group are presented in Table 1.

2.5 | Statistical analysis

To analyse the PROD-screen responses in aggregate we conducted a factor analysis using the *mirt* package (v. 1.34; Chalmers, 2012) in R (v. 4.1.1; R Core Team, 2021) with EM extraction and standard settings. The latent factor model included item threshold parameters (item type '2PL'), to obviate artefacts from widely varying item endorsement rates. Items were assigned to the three factors identified in our previous study (Therman et al., 2011) by their greatest loading in that explorative finding as follows: positive symptoms (11 items), negative symptoms (4 items), and General symptoms (5 items). One item (feeling euphoric or especially competent and important) was excluded from the subdimensions because it was not sufficiently associated with any factor. Factor scores were estimated with the *expected* a posteriori method. To create dichotomous predictors corresponding to individual symptoms, factor scores were dichotomized with cut-offs set to produce indicator frequencies corresponding to the mean endorsement rate of the items on that factor. For example, the cut-off for the negative factor was set to classify 8.8% of the respondents as being at higher risk, as this was the average rate of Yes responses to the four negative items.

Our main analysis was to compare the predictiveness of each PROD-screen symptom and dichotomized factor scores for psychosis and other psychiatric disorders using logistic regression, reporting odds ratios (OR) with 95% confidence intervals (CI). Models were adjusted for gender, parental psychiatric disorder, family structure, parental educational level, and the adolescent's cannabis use. In the analysis of individual symptoms, we considered p values below .05 to be statistically significant, and corrected for multiple testing with the Bonferroni method.

In addition, we also compared individual symptoms and factor scores of the PROD-screen between the psychosis and no disorder groups with the same modelling as in the main analysis. We did not consider statistically significant findings between psychotic and non-psychotic disorder groups notable if there was no difference between psychotic and no disorder groups. Items used for screening psychosis should differentiate psychotic and normal population.

2.6 | Attrition analysis

We describe the flow chart of the study and attrition in Figure 2. In the year 1986 the NFBC1986 was launched, when the pregnant mothers of the cohort members were first contacted. The adolescent field study of the NFBC1986 was conducted at the age of 15–16 years including the PROD-screen. Of the participants, 1466 did not consent to the field study and 1126 responded to less than 18 of the PROD-screen items. Of the original NFBC 1986 cohort ($N = 9479$), 6638 participants (70.0%) responded to the PROD-screen at the 15–16-year follow-up. In the current study, the NFBC1986 participants who had not taken part in the follow-up ($N = 1126$), denied

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TABLE 1 Sociodemographic factors for participants in different psychiatric groups

Psychiatric disorder				
	Psychotic	Non-psychotic	None	
	$N = 63$	$N = 157$	$N = 5251$	Psychotic versus non-psychotic disorder
Confounder	*N* (%)	*N* (%)	*N* (%)	χ^2 (*p* value)
Gender				
Male	38 (60.3)	82 (52.2)	2532 (48.2)	0.88 (.346)
Female	25 (39.7)	75 (47.8)	2719 (51.8)	
Cannabis use				
Never	55 (87.3)	134 (85.4)	4985 (94.9)	0.03 (.872)
Ever	8 (12.7)	32 (14.6)	266 (5.1)	
Family structure				
Living with two parents	47 (74.6)	108 (68.8)	4194 (79.9)	0.48 (.490)
Other	16 (25.4)	49 (31.2)	1057 (20.1)	
Parental psychiatric disorder				
No	54 (85.7)	122 (77.7)	4759 (90.6)	1.34 (.248)
Yes	9 (14.3)	35 (22.3)	492 (9.4)	
Parental highest education				
Basic	2 (3.2)	9 (5.7)	179 (3.4)	2.34 (0.301)
Secondary	32 (50.8)	63 (40.1)	2103 (40.0)	
Tertiary	29 (46.0)	85 (54.1)	2969 (56.5)	

the disclosure of information ($N = 2$), answered less than 18 items on the 21-item PROD-screen ($N = 4$), or had been treated in an inpatient setting with a psychiatric diagnosis at any time before the beginning of the follow-up ($N = 181$) were excluded from the statistical analyses. In the analyses of crude models there were total of 6451 participants. In adjusted analyses, participants who had missing items on confounding factors were excluded ($N = 980$), leaving 5474 participants to the final sample (Figure 2).

The drop-out rate in the crude model analyses was 35% ($N = 1726$) among males and 28% ($N = 1301$) among females. Non-participation at the 15–16-year baseline phase was the main source of attrition. Among those who were hospitalized for psychosis during the follow-up, the drop-out rate was 44% ($N = 59$), among those who were hospitalized for non-psychotic disorders the respective drop-out rate was 47% ($N = 181$), and among those without psychiatric hospital care it was 31% ($N = 2788$).

3 | RESULTS

There were no statistical differences in sociodemographic factors between the psychiatric disorder groups (Table 1). When comparing psychotic psychiatric disorders to no disorder group, psychotic patients had used cannabis more often than no disorder group ($\chi^2 = 5.94$, $p = .015$).

Of the followed participants, 1.1% ($N = 74$) developed a psychotic and 3.2% a non-psychotic psychiatric disorder during the follow-up period in the years 2003–2016 (Table 2, Figure 1). Of the participants with psychosis, 20 received a diagnosis of schizophrenia or schizoaffective psychosis, 8 were diagnosed with affective psychosis, and 64 had some other psychosis diagnosis. Non-psychotic diagnoses included 71 participants with substance use disorder, 61 with non-psychotic mood disorder, and 127 with some other non-psychotic disorder.

When comparing separate PROD-screen symptoms among those having had psychiatric hospital treatments, we found two positive symptoms and one negative symptom specifically associated with psychotic disorders in comparison to non-psychotic mental disorders (Table 3). The positive symptoms were 'Difficulty in controlling one's speech, behaviour or facial expression while communicating' (adjusted OR 4.00, 95% CI 1.66–9.92) and 'Difficulties in understanding written text or heard speech' (adjusted OR 2.25, 95% CI 1.12–4.51). The negative symptom was 'Difficulty or uncertainty in making contact with other people' (adjusted OR 2.20, 95% CI 1.03–4.67). Of these three symptoms, one positive symptom ('Difficulty in controlling one's speech, behaviour or facial expression while communicating') remained statistically significant after Bonferroni correction for multiple comparisons.

One general symptom in the PROD-screen had an OR <1.00 ('Worrying, nervousness or anxiety'). One symptom ('Feeling euphoric or especially competent and important') had statistically significant association with psychosis onset, but it did not manage to differentiate psychosis prone participants from general population without hospital treated mental disorders.

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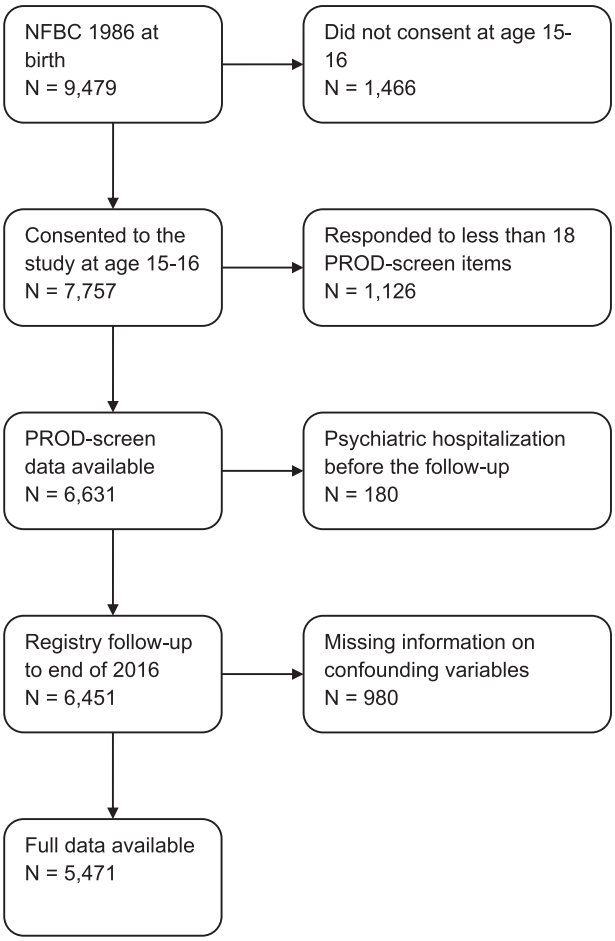

FIGURE 2 Flowchart of the study

TABLE 2 Numbers and cumulative incidences (%) of first episode psychotic and non-psychotic disorders during 2003–2016 follow-up by gender and in total

	All	Male	Female
Psychiatric disorders	***N* = 6451**	***N* = 3165**	***N* = 3286**
Psychotic	74 (1.1%)	47 (1.5%)	27 (0.8%)
Non-psychotic	206 (3.2%)	107 (3.4%)	99 (3.0%)

Levels of positive, negative, and general PROD-screen symptoms did not differ in the psychotic disorder group compared to the non-psychotic psychiatric disorder group (Table 4).

We also compared psychosis to no disorder in an additional, exploratory analysis (Tables S1 and S3).We found five positive and three negative symptoms that predicted later hospital-treated psychotic disorder when comparing to no disorder group (Table S2). Two of the five positive symptoms remained significant after Bonferroni-correction ('Difficulties in understanding written text or speech heard' and 'Difficulty in controlling one's speech, behaviour or facial expression while communicating') as well as two of the three negative symptoms ('Difficulty or uncertainty in making contact with other people' and 'Lack of initiative or difficulty in completing tasks').

4 | DISCUSSION

In this general-population-based prospective birth cohort study, we found that three symptoms of the PROD-screen when reported in adolescence specifically predicted the subsequent onset of psychosis and one of them remained statistically significant after the very conservative Bonferroni correction.

The symptoms that predicted psychosis in our study were present in the BSABS (Difficulty in controlling one's speech, behaviour or facial expression while communicating), both the SIPS and the BSABS (Difficulties in understanding written text or heard speech) and in the SIPS, the IRAOS, and the BSABS (Difficulty or uncertainty in making contact with other people), respectively (Heinimaa et al., 2003). These symptoms are all related to social interaction and communication.

These findings are in line with other prospective general population follow-up studies (Dominguez et al., 2010; Poulton et al., 2000). In the Dunedin Study birth cohort, self-reported psychotic symptoms—both positive and negative—at age 11 predicted a very high risk of a schizophreniform psychosis diagnosed by structured interviews at age 26 years (Poulton et al., 2000), though a later analysis showed that this association was not specific. When comparing our study to the Dunedin study, we had a different setting. Outcome variables were based on an interview in the Dunedin study while ours were clinical diagnoses. The Dunedin study's control group included no disorders, and our study included specifically non-psychotic psychiatric disorders as a control group. Another longitudinal prospective study was conducted among adolescents and young adults from Munich aged 14–24 years. There, negative symptoms predicted positive features and were associated with later psychotic disorder (Dominguez et al., 2010).

As psychotic disorders are relatively rare, it has been emphasized that it may be impossible to predict development of psychosis in the general population (Lee et al., 2018). It is also uncertain whether early-stage treatment of prodromal symptoms reduces the conversion rate to psychosis (Fusar-Poli et al., 2020; Lieberman et al., 2019), so applying the present results to screening is premature. The main contribution of our study to the existing literature is the study setting with a population-based, prospective data collection and long follow-up, and the availability of the comprehensive CRHC data allowing the comparison of respondents who later developed a psychosis not only to healthy comparison participants but especially to those who developed some other hospital-treated psychiatric disorder.

4.1 | Strengths and limitations of the study

4.1.1 | Strengths

Strengths of the present study include the prospective setting, a large general population birth cohort sample, the participants being of the same age and born in same geographical area, both genders being

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TABLE 3 Numbers and prevalences of PROD-screen psychotic-like symptoms reported at ages 15–16 and their predictiveness of later hospital-treated psychotic and non-psychotic disorders during the years 2003–2016

			Logistic regression estimates					
			Psychotic disorder	Non-psychotic disorder	Psychotic versus non-psychotic disorder			
Experience	Responses *N*	Experience: Yes, *N* (%)	*n* (%)	*n* (%)	Crude OR (95% CI)	*p* value	Adjusted[a] OR (95% CI)	*p* value
Positive symptoms:								
5. Difficulties in thinking clearly or concentrating, interfering thoughts or thoughts interrupted	6417	2252 (35.1)	33 (44.6)	85 (41.3)	1.15 (0.67–1.98)	.6	1.34 (0.73–2.48)	.347
6. Difficulties in considering alternatives or in making even minor decision	6390	1641 (25.7)	19 (25.7)	59 (28.6)	0.86 (0.46–1.55)	.621	0.76 (0.37–1.51)	.442
7. Experience of thoughts running wild or difficulty in controlling the speed of thoughts	6407	1287 (20.1)	19 (25.7)	48 (23.3)	1.17 (0.62–2.15)	.612	1.23 (0.61–2.43)	.564
8. Difficulties in understanding written text or speech heard	6421	1077 (16.8)	23 (31.1)	40 (19.4)	1.85 (1.00–3.36)	.045	2.25 (1.12–4.51)	.022
10. Difficulty in controlling one's speech, behaviour or facial expression while communicating	6426	504 (7.9)	16 (21.6)	16 (7.8)	3.24 (1.52–6.93)	.002*	4.00 (1.66–9.92)	.002*
14. Feeling that events in the environment or other people's behaviour specifically concern oneself	6414	1198 (18.7)	17 (23.0)	39 (18.9)	1.28 (0.66–2.42)	.447	1.45 (0.66–3.10)	.345
16. Disorders in connection with vision	6427	887 (13.8)	16 (21.6)	31 (15.0)	1.54 (0.77–2.98)	.209	1.30 (0.60–2.71)	.492
17. Disorders in connection with hearing	6425	510 (7.9)	10 (13.5)	24 (11.7)	1.18 (0.52–2.55)	.674	1.08 (0.39–2.75)	.872
19. Feeling that something strange or inexplicable is taking place in oneself or in one's environment	6408	435 (6.8)	12 (16.2)	18 (8.7)	2.01 (0.90–4.37)	.081	1.50 (0.62–3.51)	.355
20. Feelings, thoughts or behaviours that could be considered weird or peculiar	6402	915 (14.3)	23 (31.1)	37 (18.0)	2.06 (1.11–3.78)	.02	1.95 (0.94–4.00)	.067
21. Feelings that one is being followed or being influenced in some special way	6408	365 (5.7)	10 (13.5)	16 (7.8)	1.85 (0.77–4.22)	.152	1.25 (0.44–3.24)	.657
Negative symptoms:								
11. Difficulty or uncertainty in making contact with other people	6431	631 (9.8)	19 (25.7)	31 (15.0)	1.95 (1.01–3.7)	.043	2.20 (1.03–4.67)	.040
12. Lack of initiative or difficulty in completing tasks	6424	806 (12.5)	20 (27.0)	34 (16.5)	1.86 (0.98–3.48)	.053	1.63 (0.78–3.35)	.190

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TABLE 3 (Continued)

Experience	Responses *N*	Experience: Yes, *N* (%)	Logistic regression estimates: Psychotic disorder *n* (%)	Non-psychotic disorder *n* (%)	Psychotic versus non-psychotic disorder: Crude OR (95% CI)	*p* value	Adjusted[a] OR (95% CI)	*p* value
13. Social withdrawal, for example avoidance of company, feeling better in solitude	6424	702 (10.9)	14 (18.9)	32 (15.5)	1.26 (0.62–2.48)	.511	1.16 (0.52–2.47)	.704
18. Difficulties in carrying out ordinary routine activities (at least 1 week)	6424	135 (2.1)	6 (8.1)	7 (3.4)	2.5 (0.78–7.77)	.111	2.01 (0.47–8.15)	.324
General symptoms:								
1. Worrying, nervousness or anxiety	6442	1940 (30.1)	22 (29.7)	89 (43.2)	0.56 (0.31–0.97)	.044	0.45 (0.23–0.89)	.023
2. Trouble with sleep or loss of appetite	6431	996 (15.5)	13 (17.6)	53 (25.7)	0.61 (0.30–1.17)	.153	0.61 (0.26–1.35)	.233
3. Bodily restlessness, for example pacing up and down, not being able to sit still	6434	568 (8.8)	9 (12.2)	38 (18.4)	0.61 (0.26–1.28)	.213	0.56 (0.21–1.33)	.212
4. Difficulty in coping with stress related to ordinary daily life events	6404	1155 (18.0)	20 (27.0)	53 (25.7)	1.08 (0.58–1.96)	.797	0.98 (0.47–1.99)	.959
9. Depression, apathy, loss of energy or marked tiredness	6422	1548 (24.1)	23 (31.1)	73 (35.4)	0.82 (0.46–1.44)	.499	0.69 (0.33–1.39)	.304
Other symptoms:								
15: Feeling euphoric or especially competent and important	6389	2809 (44.0)	35 (47.3)	75 (36.4)	1.63 (0.94–2.8)	.079	2.01 (1.09–3.74)	.026

[a]Adjusted for gender, any parental psychiatric disorder before 2003 (yes vs. no), family structure at age 16 (living with one vs. two parents), parental educational level, own cannabis use in adolescence (never vs. ever).
*Statistically significant at Bonferroni-corrected overall *p* value <.05.

TABLE 4 Number of and cumulative incidences of new cases of psychotic and non-psychotic disorders by psychotic-like symptom dimension: Positive, negative, and general

Symptom dimension	Yes, *N* (%) *N* = 6451	Psychotic disorder *N* (%) *N* = 74	Non-psychotic disorder *N* (%) *N* = 206	Psychotic versus non-psychotic disorder: Crude OR (95% CI)	*p* value	Adjusted[a] OR (95% CI)	*p* value
Positive	997 (15.5)	24 (32.4)	48 (23.3)	1.58 (0.87–2.82)	.125	1.36 (0.74–2.51)	.325
Negative	560 (8.7)	18 (24.3)	33 (16.0)	1.69 (0.87–3.2)	.115	0.73 (0.35–1.45)	.384
General	1242 (19.3)	20 (27.0)	65 (31.6)	0.8 (0.44–1.43)	.468	1.25 (0.62–2.47)	.529

Note: Sensitivity to detect psychosis prospectively was 41% for any positive psychotic-like symptoms, with a specificity of 72%, and a positive predictive value (PPV) of 2%. Negative symptoms sensitivity 55%, specificity 76%, and PPV 3%. General symptoms sensitivity 51%, specificity 55%, and PPV 1%.
[a]Adjusted for gender, any parental psychiatric disorder before 2003 (yes vs. no), family structure at age 16 (living with one vs. two parents), parental educational level, own cannabis use in adolescence (never vs. ever).

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included (Table 2), use of valid instruments to measure symptoms in adolescence, using the comprehensive nationwide CRHC, use of a comparison group of hospital treated non-psychotic cases, and including several confounding factors. We had an opportunity to test the symptoms of the PROD-screen in adolescence and their association with first-episode psychosis in a general population of young people over a long time, taking symptom specificity to psychosis into account. Previous studies have mainly concentrated on psychiatric outpatients and help-seeking individuals with a large variation in age (Daneault et al., 2013; Lee et al., 2018) and no previous study has examined the predictive capacity of conversions to psychosis using the PROD-screen.

The number of the youth returning the questionnaires could be considered sufficient to represent the general youth population of Northern Finland, as the cohort follow-up included 6634 participants who had filled in the PROD-screen.

4.1.2 | Limitations

Our register follow-up only included hospital-treated mental disorders, and we excluded those at-risk individuals who had previous substance abuse and other mental illnesses. Because psychiatric disorders requiring hospitalization are relatively rare, the numbers of adverse outcomes remained quite small despite the large original cohort population. The follow-up period was from 2003 to 2016. Some additional psychotic disorders will emerge over the coming years, which may alter symptom predictiveness, though predictiveness is likely to drop over time.

The PROD-screen was used as a mailed self-report questionnaire. The participants answered these statements at home. It is therefore possible that some of the statements might have been misconstrued. As Poulton et al. (2000) noted, even structured interviews have been criticized for detecting not only clinical psychosis but also false positive cases (Anthony et al., 1985; Helzer et al., 1985; Kendler et al., 1996), and self-report questionnaires do not allow for follow-up clarifications.

Furthermore, even though the CRHC has been found to be quite reliable in detecting psychoses (Isohanni et al., 1997; Mäkikyrö et al., 1998), for non-psychotic mental disorders it is a rough measure. For this reason, we are unsure whether the results of our study may be generalized to non-psychotic mental disorders that do not require hospitalization. Our study did not include outpatient patients because we wanted to have more severe cases and better reliability of diagnoses (Isohanni et al., 1997; Mäkikyrö et al., 1998). Disorders treated in outpatient settings are generally less severe than hospital-treated, but only minority of psychotic disorders are missed by using hospitalization data only (Perälä et al., 2007). If outpatient diagnoses would have been included in this study, some more individuals from the no disorder group would have moved to the non-psychotic psychiatric disorder group.

One of the limitations, as with many longitudinal studies, is the possibility of selection bias caused by the substantial attrition over time (Zammit et al., 2013). In the present study, two thirds of the original birth cohort participated in the 15–16-year field study. In the Northern Finland Birth Cohort 1966 study, those with any psychiatric disorder participated less actively than those without psychiatric disorder (Haapea et al., 2008). However, there was minimal attrition in the follow-up as we used national register data.

The PROD-screen includes questions from the SIPS/SOPS, IRAOS, and BSABS structured interviews (Heinimaa et al., 2003). The included putative psychosis-risk symptoms are common in the general young population, and the Yes/No-response format is relatively non-informative, resulting in a low positive predictive value for the PROD-screen, as it has a limited number of symptoms. This hampers the clinical applicability of the finding; therefore, it is necessary to employ more specific questionnaires and interviewing methods for the early detection of psychosis, and/or combine questionnaires with other measures, such as biomarkers, in the future (Murray et al., 2021; Therman et al., 2011).

4.2 | Conclusions and clinical implications

To our knowledge, this is the first general-population-based prospective study of adolescents exploring psychiatric symptoms predicting specifically the onset of hospital-treated first episode psychosis in comparison to non-psychotic disorders. We found three symptoms related with difficulties in social interaction which predicted onset of psychosis. Of these three symptoms, one positive symptom ('Difficulty in controlling one's speech, behaviour or facial expression while communicating') remained statistically significant after Bonferroni correction for multiple comparisons. This is a novel finding and should be replicated.

Psychosis-risk symptoms appear less common when assessed with gold-standard interviews rather than with self-reports, and PLEs are thus overreported with questionnaires (Horwood et al., 2008). This study helps healthcare workers identify specific symptoms predicting psychosis. Our present results indicate that social interaction symptoms are associated specifically with onset of psychosis.

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DATA AVAILABILITY STATEMENT

NFBC data is available from the University of Oulu, Infrastructure for Population Studies. Permission to use the data can be applied for research purposes via electronic material request portal. In the use of data, we follow the EU general data protection regulation (679/2016) and Finnish Data Protection Act. The use of personal data is based on cohort participant's written informed consent at his/her latest follow-up study, which may cause limitations to its use. Please, contact NFBC project center (NFBCprojectcenter(at)oulu.fi) and visit the cohort website for more information.

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